The Role of Substance P in Neurodegenerative Diseases

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Abstract- Tachykinins (TKs) are a family of neuropeptides widely distributed in the human body, especially in the nervous system. TKs have exhibited both neuroprotective and neurodegenerative properties in the central nervous system (CNS) and spinal cord. Also, several studies have shown that substance P (SP), as a pioneering neuropeptide of the TK family, is engaged in the pathogenesis of neurodegenerative disorders (NDs), such as Alzheimer disease, Multiple Sclerosis, Parkinson's disease, Huntington's disease, and Amyotrophic lateral sclerosis. However, a huge body of information available about the level of SP in NDs demonstrates that SP and its receptors might be prognostic or diagnostic factors for NDs. The present review article summarizes the roles of TKs in common neurodegenerative disorders.

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Keywords: Tachykinins; Tachykinin receptors; Substance P; Neurodegenerative disorders

Introduction

Some neurological disorders with an unknown etiology are unique to the human nervous system. Neurodegenerative disorders (NDs) such as Alzheimer's disease (AD), Parkinson's disease (PD), Multiple Sclerosis (MS), Huntington's disease (HD), and Amyotrophic lateral sclerosis (ALS) are assessed by clinical criteria, laboratory investigations, and functional neuroimaging (1-3). The diagnostic accuracy of these diseases varies depending on the type of neurodegenerative disease. In many cases, the diagnosis remains unknown until death; and during the course of the disease, NDs can be improved by medications but never cured (4). Therefore, the expansion of biomarkers that may evaluate the risk of disease, presence, and progression is one of the major aims and challenges in research on NDs. In this regard, there are no confirmed biomarkers that can be used to reliably diagnose NDs or prevent their progression with high sensitivity and specificity. Thus, a large number of biomarkers may be required to detect these patients. Recently, several studies on NDs have suggested that TKs, as a diagnostic biomarker for NDs, might play important roles in CNS since they have both neuroprotective and neurodegenerative properties (5,6). Therefore, the purpose of this review article is to summarize the roles of TKs in common NDs such as AD, MS, PD, HD, and ALS.

Mammalian tachykinins

Tachykinins are a family of neuropeptides (10-11 amino acids) characterized by a conserved motif (Phe-X-Gly-Leu-Met-NH2) in their C-terminal (7,8). Several TK peptides have been identified in mammalian cells including substance P (SP), hemokinin-1 (HK-1), neurokinin B (NKB), neurokinin A (NKA), and N-terminally extended forms of NKA such as neuropeptide K (NPK) and neuropeptide γ (NPγ) (9). Generally, three genes are responsible for coding these neuropeptides, including Tac1 (pre-pro-tachykinin-A, Ppt-a), Tac3 (Ppt-b), and Tac4 (Ppt-c). SP, NKA, NPK, and NPγ are encoded by Tac1 while NKB and HK-1 are encoded by Tac3 and Tac4, respectively (10). These neuropeptides are mainly expressed in the nervous and immune systems (9,11,12). SP and NKA are released from the nerve endings in the spinal cord and peripheral nerves, acting as excitatory neurotransmitters. Although SP is often expressed in enteric neurons, it can be produced in immune cells during inflammatory processes, as well. NKB is present in the central nervous system (CNS) and spinal cord. In addition, HK-1 is a novel SP-like peptide that exists in non-neuronal cells and tissues (8,9,11,13).

The effects of TKs by interacting with specific

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receptors, named neurokinin 1 receptor (NK1R), NK2R, and NK3R (8,14). These receptors, as small proteins belonging to the family of G protein-coupled membrane receptors (GPCRs), contain 350 to 500 amino acids. Each TK peptide prefers binding to a specific receptor with a higher affinity than any other TKs (15,16). For instance, SP and HK-1 prefer to interact with the NK1 receptor, while NKA and NKB have a higher affinity for the NK2R and NK3R, respectively (9,10,16). After binding of TKs to their receptors, it has been shown that they utilize the phospholipase C system as a second messenger. The activated phospholipase C leads to the hydrolysis of phosphoinositol and increased intracellular calcium levels (17). Subsequently, the activation of TK receptors causes various biological activities, including neurogenic inflammation, hematopoiesis, smooth muscle contraction, emotional behavior, vasodilation, immune system activation, pain transmission, and stimulation of endocrine gland secretion (14,18,19). Besides, they are involved in the pathophysiology of several diseases, such as breast and endometrial cancer (20,21).

The effect of tachykinins in neurodegenerative diseases

NDs are chronic and progressive diseases associated with selective and symmetric loss of neurons in motor, sensory, or cognitive systems (22). Although there is still no evidence of the neuropathic role of a specific neuropeptide in a particular ND, some neuropeptide levels might change in some of these disorders (23-26). Moreover, it has been shown that TKs can have neurotrophic effects on central neurons and NDs, probably due to the absence or loss of TKs in selected regions of the brain and spinal cord (19). SP was recognized as the first neuroactive TK and was the first one suggested to be a neurotransmitter (27). In addition, it has frequently shown a widespread distribution in the CNS of mammals, including humans, and has been detected with different effects in normal and pathological conditions (28,29). In this paper, it is hypothesized that SP as an important member of the TKs family, shows a neurotrophic activity on central neurons, and the defects involving SP in the selected regions may lead to various NDs (as shown in Figure 1).

Alzheimer disease (AD)

AD is one of the irreversible neurodegenerative disease, which is clinically characterized by progressive impairments of memory and cognition and the neuronal loss in the various regions of the brain (30). Histopathologically, several studies have suggested that the hallmarks of AD are the accumulation of insoluble beta-amyloid (Aβ) fibrils in senile plaques that play an important role in the onset and development of the disease (31-33). Aβ is one of the main components of senile plaques in AD (34) that a special segment of it (amino acids 1 to 40) has been shown to mediate both neurotrophic and neurotoxic properties. In this line, Yankner *et al*., showed that Aβ (amino acids 1 to 40) exhibits neurotrophic effects in undifferentiated rat embryonic hippocampal neurons in low concentrations, while it has neurotoxic effects at high concentrations. Neuronal degeneration may occur in mature neurons as a result of the accumulation of high Aβ concentrations, as occurs in AD (35). Moreover, the association of TKs with AD was first proposed by Yankner *et al*., who determined that some sequences of Aβ (amino acids 25 to 35) have homology to SP, and this sequence could function as SP antagonists. In addition, according to Kowall *et al*., the partial sequence of Aβ (25-35) might have the ability to act as an SP antagonist by interacting with its SP receptors (36).

In contrast to these studies, several studies have demonstrated the lack of any interaction between Aβ and SP receptors (37,38). This view is supported by Kimura *et al*., who observed that Aβ (1-40) could only weakly activate the SP receptors, whereas, in the presence of glutamate as a synergist, it enhances SP receptors activation in vitro (39). Aβ, along with glutamate, stimulates phosphatidylinositol production and subsequently increases intracellular calcium, which ultimately leads to neuronal cell death (40,41). In this context, El-Agnaf *et al*., also reported that Aβ (25 to 35) has the same properties as SP in the presence of phenylalanine at position 31, whereas it reverses these properties after replacement of phenylalanine with an isoleucine residue at this position (34).

It is also well established from a variety of studies that SP in the brain plays a positive role in memory and learning processes, which is probably because of an increase in the effect of dopamine neurotransmitters in synaptic spaces. According to this study, the reduction or lack of SP expression possibly involves in the pathogenesis of AD (42). In most studies of AD patients, decreased the level of SP immunoreactivity is reported in different parts of the brain cortex in patients group compared to the control group (43,44). In addition, both depletion and increased SP in CSF have been observed in manifest AD (45-48). Moreover, several lines of evidence suggest that the reduction in SP level may occur in the neurons that are subject to choline acetyltransferase activity reduction as a specific biochemical feature in the

AD, or maybe due to several simultaneous changes in the neurochemical systems in this disease (49,50). Moreover, the hydrolysis of SP is also reported in AD as a reason for the reduction of SP level. The degradation of SP is catalyzed by the enzyme prolyl endopeptidase (PEP), which cleaves the SP's proline residue from the C-terminal (51). The literature on PEP has highlighted that the enzyme is involved in the formation of Aβ, and its activity is higher in AD patients (52,53). In contrast with these findings, some studies have reported the lack of any significant difference in the level of SP in the AD patients compared to the control group. These different results seem to depend on the type of population despite the many studies conducted to confirm the decreased level of SP in AD (54,55).

Multiple sclerosis (MS)

Multiple sclerosis (MS) is a common neurological and autoimmune disorder typically characterized by focal regions of inflammation, demyelination, and gliosis in the grey matter of the CNS (56,57). Both innate and adaptive immune responses play a key role in the development of MS, but it is mainly affected by T cells (of Th1, Th17) (58,59). Previous studies have reported that SP can play an essential role in activating autoimmune T cells by increasing pro-inflammatory cytokine production, which can up-regulate SP and NK1R expression, and incite antigen-presenting cells to produce more T cell stimulatory cytokines (60-62). For instance, Vilisaar *et al*., proposed a model whereby immunocyte derived SP stimulates migration of Th1 and Th17 autoreactive cells to the CNS through the blood-brain barrier (BBB) by increasing pro-inflammatory cytokines including IL-12 and IL-23 (63). In addition, SP may enhance the permeability of BBB by interacting with NK1R on endothelial cells that allow an influx of immune mediators and activated T cells to the CNS, which can interact with astrocytes and oligodendroglia, leading to further release of cytokines and SP (64,65). Thereafter, SP can act via NK1R on the various cellular components of the MS plaque, such as lymphocytes, macrophages, and glia, to increase proliferative and pro-inflammatory responses. An increase in the level of SP can lead to the progression of inflammation to demyelination and gliosis (56). Further study was accomplished in order to clarify the role of the SP/NK1R system in the MS and interpretation of results showed that this system could contribute to the augmentation of CNS inflammation in MS (66). Also, they concluded that treatment with NK1R antagonists might improve the success of the treatment of MS.Furthermore, Kostyk *et al*., examined alterations in the expression of SP in patients with MS and showed that the expression of SP in astrocytes at the plaque site significantly increased compared to the control group (67). In contrast, Rösler *et al*., reported that the level of SP in the CSF tended to increase in all subgroups of MS patients, but showed no significant differences with the control group (68).

Parkinson's disease (PD)

PD is a progressive ND that is characterized by the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc) (69). Various secondary disorders occur due to the degeneration of dopaminergic neurons, e.g., inflammation, BBB dysfunction, oxidative stress, glutamate excitotoxicity, and mitochondrial dysfunction (70). The current treatment for PD is L-3,4-dihydroxyphenylalanine (L-DOPA). This product does not prevent the degeneration of neurons and, at the same time, replaces the lost dopamine and prevents its breakdown (71). It has been determined that L-DOPA causes a change in the signaling pathways of the brain and may also lead to abnormal involuntary movements in the patients (72). In recent years, several efforts have been focused on extending new neuroprotective therapies in order to treat the main cause of PD. Previous studies have recognized the SP and its receptor (NK1R) as new neuroprotective targets (71,73). In this context, several investigations have provided multiple conclusions from measurements of SP level in the CSF of PD patients. Nutt *et al*., reported that the level of SP is decreased slightly in their CSF samples (74). On the other hand, Pezzoli *et al*., found that the level of SP is increased in Parkinson patients with severe disability compared to non-symptomatic neurological controls (75). However, a study by Cramer *et al*., showed a lack of any significant difference between patients with PD and the control group in the CSF level of SP (76). The reason for such different results might be due to the type of patients studied or the cross-reactivity of the radioimmunoassay technique used for the determination of SP (77).

In brain regions, the detection was almost consistent. The findings showed that the SP level is significantly decreased in substantia nigra-pars compacta and pars reticulata (78-80). Nevertheless, the researchers have recognized the lack of any relation between the reduction of SP level and intensity of the disease (80). A considerable amount of studies has been conducted to determine the pathology of PD and found that the primary event of PD is the loss of SP activity in the substantia nigra (SN). These studies introduce a lack of dopamine as a secondary response (81). In contrast, another research

reported that the lack of dopaminergic drive leads to the reduction of SP expression in the SN. Also, they found that in the early stage of PD, in which dopamine neurons remain, the SP expression in the SN is normal or even elevated (82). To determine the effects of SP, Thornton *et al*., (2012) demonstrated that the enhancement of SP level accelerates disease progression, whereas treatment with NK1R antagonists preserves dopaminergic neurons and maintains BBB integrity in vitro. In addition to the mentioned results, they also found that the SP receptor antagonist alleviates neuroinflammation and induces the progression of motor function (73).

Other neurodegenerative diseases

A number of other NDs, such as Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS), have been studied for alterations in TKs levels. HD is an autosomal dominant neurological disorder related to the dysfunction and degeneration of some parts of the brain, especially in the ganglia basal region (83). In the clinical course, the disease is accompanied by brain weight loss, a substantial reduction in basal ganglia size, and atrophy of brainstem regions (84). Moreover, in this disease, there is a decrease in the number of neurotransmitters, like SP, especially in the SN and basal ganglia. In other parts of the brain, such as thalamus and hypothalamus, there is no significant difference in the concentration of SP between patients and healthy groups (83). Several investigations have shown that SP could increase the release of striatal dopamine by sending a projection to the SN, and SP-containing striatal neurons can have a feedback loop with dopaminergic input (85,86). Accumulating evidence revealed that the SP might directly or indirectly affect the modulation of the sterility neurons function (87). In fact, the reduction of SP level is the first change in the level of neuropeptides in HD (88). Beal *et al*., were the first who studied the SP level at the core of the stria terminalis and the subthalamic nucleus. They found that there is a considerable reduction in SP-like immunoreactivity (SPLI) in both regions; indeed, SP-depletion is the first case of neurochemical deficiency found in subthalamic cores in HD (87). In a study, immunohistochemistry was tested on patients with HD and found that the level of SP is decreased significantly in the SN and globus pallidus (89). Similarly, Gale *et al*., showed that the concentration of SP in the SN and globus pallidus is significantly reduced in Huntington patients compared to controls (90).

Amyotrophic lateral sclerosis (ALS) is another ND, which is associated with changes in the SP level in the CNS. However, studies on this disease are limited and, therefore, difficult to conclude. ALS is an ND that primarily targets the motor neurons of the CNS (91). Its symptoms are the combination of the lower motor neuron (i.e., wasting, fasciculation, and hypotonia) and upper motor neuron signs (i.e., hypertonia, spasticity, and weakness) (92). Several lines of evidence suggest that the main cause of the onset and progression of ALS is still unknown (93), but there is growing evidence that the level of SP as a biomarker may be affected in this disease. CSF biomarkers such as SP could represent neuronal cell loss at an early stage of the disease. For example, Matsuishi *et al*., reported that the concentration of SP in the CSF of ALS patients was higher than in control groups (94). Furthermore, in another study, the distribution of NK1R was detected at the spinal cord of ALS patients. Also, they showed a significant reduction in SP binding, especially in the ventral horn that is associated with the loss of motor neurons. The results of this study suggested that the localization of receptors of SP to the ventral horn motor neurons in the human spinal cord that can justify the role of SP in the function of motor neurons in the disease (95). In addition, Gilberg *et al*., demonstrated that there is no significant decrease in the level of SPLI in patients with ALS, but the level of SPLI tends to decrease compared with a control group (96). In summary, there is slight evidence to show the changes in the SP level and its receptors in the ALS disease or to consider its changes as a secondary conclusion of the loss of motor neurons.

Regarding the vast distribution of TKs and TK receptors in the specific regions of the brain and spinal cord in addition to their participation in various types of inflammatory and immune diseases, the present study was conducted to summarize the effects of TKs on NDs. There are many investigations that show the roles of TKs in NDs. From the studies conducted in this regard, some conflicting results have been reported. However, these studies have majorly shown that SP is the most important factor in neurological diseases among the TK family. In the investigations discussed above (as summarized in Table 1), the reduction of SP level has been identified as a primary event in NDs, even though there is not enough information to support the view that the loss of SP is the main event in any of these disorders. In contrast, the existing literature on the change of SP level has also highlighted that the alteration of SP concentration is a secondary change in NDs, but there is not enough data to guarantee this view. Based on the findings reported in this manuscript, SP level, and its receptor (NK1R) are known as the most important prognostic and diagnostic factors in NDs. Nevertheless, the investigations listed above did not provide information about the exact roles of SP in NDs

and are full of conflicts. The question raised by the present study is, "what is the most important reason for getting different results from those observed in this article?" Hence, it is required to conduct a larger number of and more extensive studies to determine the roles of SP and other TKs in NDs.

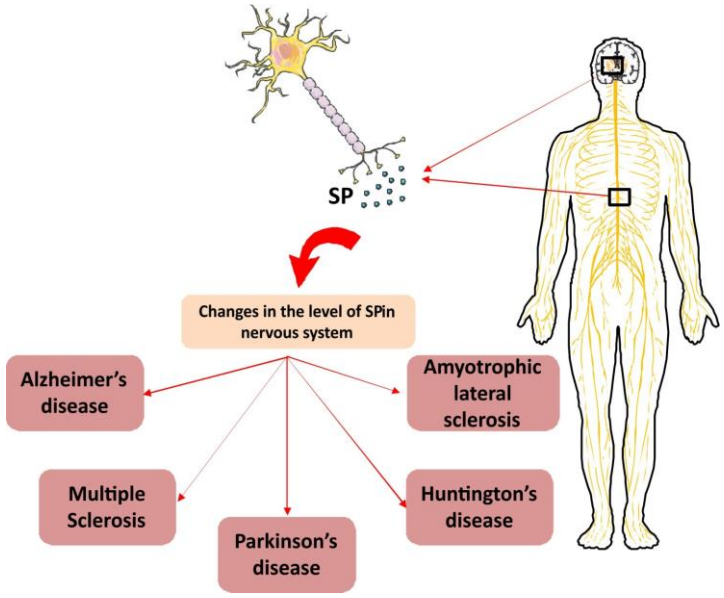

Figure 1. Alteration of SP level in various regions of the nervous system can relate to neurodegenerative disorders

Table 1. Changes in the level of SP in various Neurodegenerative disorders

Neurodegenerative disorders	Representative studies
Alzheimer disease	The level of CSF SP in AD patients is higher than patients with other dementias and healthy controls (46) SP is significantly lower in CSF of AD patients compared to controls (45). The quantitative level of SP had a relative reduction in the cerebral cortex (43). Considerable reductions in SP in various cortical areas and hippocampus in the brain of patients (44). SP significantly is lower in cerebral cortical regions of patients with clinical and pathological evidence of AD (49). No significant difference is seen in SP in the brain and spinal cord areas of AD patients compared to controls (54, 55).
Multiple Sclerosis	The expression of SP in astrocytes at the plaque site in patients with MS increased compared to the control group (67). No significant difference was observed between the subgroups of MS patients and the control group in the CSF level of SP (68). A slight, but not significantly different, reduction in CSF levels of SP (74)
Parkinson's disease	No significant difference between late-onset patients with PD and the control group in the CSF level of SP (76) Significant elevation in CSF levels of SP in Parkinson patients with severe disability compared to non-symptomatic neurological controls (75) The significant decrease in SP in the substantia nigra in postmortem brains from Parkinson patients compared to controls (78-80) The primary pathology of PD is a loss of action of SP in the substantia nigra, and the degeneration of the dopaminergic neurons is a secondary response (83). The dopaminergic neurons lead to a decrease in the nigral SP expression. But, in the early stage of PD, in which dopamine neurons remained, the nigral SP expression showed no change or even increased (73).
Amyotrophic lateral sclerosis	SP level in the CSF of ALS patients was higher than that in the control groups (94). A marked reduction in SP binding with its receptors in the ventral horn (95) No significant decrease was observed in the level of SPLI in patients with ALS, but the level of SPLI tended to decrease compared with control (96).
Huntington's disease	SP levels markedly declined in the core of the stria terminalis and the subthalamic nucleus (87). The level of SP decreases considerably in the substantia nigra and globus pallidus (89). SP levels declined in the substantia nigra and globus pallidus (90). The amount of SP in the spinal cord is not markedly reduced (74).

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